**ADIPOSE TISSUE SURFACE-EXPRESSION OF LDLR AND CD36; LINK TO RISK FACTORS FOR TYPE 2 DIABETES IN NORMOCHOLESTEROLEMIC SUBJECTS**

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**Background/Hypothesis**: LDLC-lowering variants are linked to higher diabetes risk. Underlying mechanisms are unknown; however, a role for LDL receptor (LDLR) pathway was proposed. Activation of white adipose tissue (WAT) Nucleotide-binding domain and Leucine-rich repeat Receptor containing a Pyrin domain 3 (NLRP3) inflammasome and secretion of interleukin-1 beta (IL-1β) promote WAT dysfunction and type 2 diabetes (T2D). We tested the hypothesis that 1) normocholesterolemic subjects with higher WAT surface-expression of LDLR and CD36 have higher WAT NLRP3 inflammasome activity and T2D risk factors and 2) LDL upregulate WAT NLRP3 inflammasome activity.

**Methods:**We measured in 29 subjects(LDLC<3.5 mmol/L, BMI=25-40 kg/m2) WAT surface-expression of LDLR and CD36 (immunofluorescence), WAT NLRP3 protein expression (immunoblot), WAT function as the storage of 3H-triolein-substrate*ex vivo*. Disposition index (DI) was calculated as C-peptide secretion x insulin sensitivity measured by Botnia clamps. Plasma Proprotein Convertase Subtilisin/ kexin Type 9 (PCSK9) was used as an inverse proxy for WAT surface-expression of both LDLR and CD36.

**Results**: Compared to subjects with higher than median plasma PCSK9 per sex, subjects with lower plasma PCSK9 had 2 fold higher WAT surface-expression of LDLR and CD36, lower fasting NLRP3 protein expression (-48%) but greater increase in WAT NLRP3 expression after a high-fat meal (+41%). They also had lower WAT function (1.64±0.83 *vs* 4.48±2.84 nmol 3H-TG/mg) and DI (1.07±0.20 *vs* 1.21±0.11). WAT surface-expression of LDLR was positively associated with that of CD36 and negatively with WAT function (*r*=-0.42) in all subjects (*P*<0.01). Incubation of subjects’ WAT with their own native LDL (1.2 g apoB/L) induced IL-1β secretion when added as *priming*signal in adenosine triphosphate (ATP)-stimulated WAT (ATP=0.16±0.32 vs LDL+ATP=2.72±3.76 pg/mg WAT, *P*=0.037, N=11).

**Conclusion:** Normocholesterolemic subjects with higher WAT surface-expression of LDLR and CD36 have upregulated WAT NLRP3 inflammasome *priming* and risk factors for T2D, likely induced by higher WAT-uptake of LDL. This may explain higher diabetes risk in subjects with LDLC-lowering variants.